FILE 'HOME' ENTERED AT 13:06:17 ON 13 JUL 2001

=> fil reg

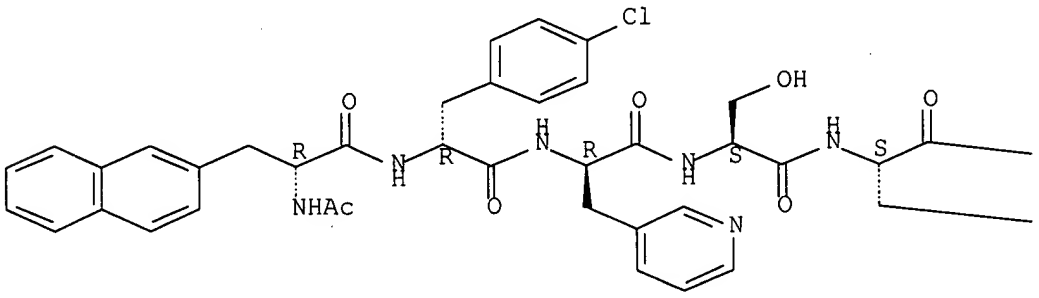
=> s cetrorelix/cn
L1 1 CETRORELIX/CN

=> d

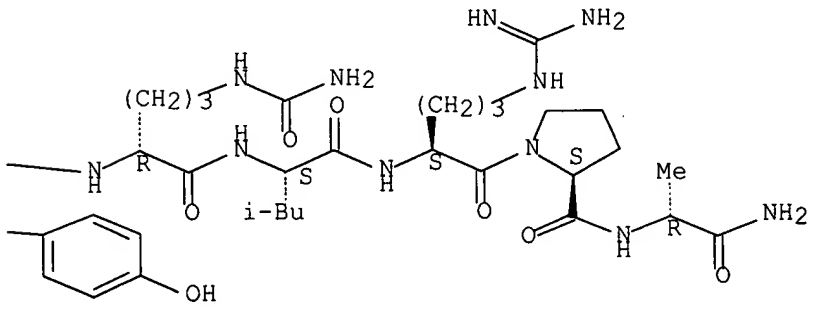
L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS
RN 120287-85-6 REGISTRY
CN D-Alaninamide, N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-L-tyrosyl-N5-(aminocarbonyl)-D-ornithyl-L-leucyl-L-arginyl-L-prolyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 3: PN: WO0018423 PAGE: 26 claimed protein
CN **Cetrorelix**
FS PROTEIN SEQUENCE; STEREOSEARCH
DR 126299-94-3
MF C70 H92 Cl N17 O14
CI COM
SR CA
LC STN Files: ADISINSIGHT, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CBNB, CHEMCATS, CIN, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PROMT, TOXLINE, TOXLIT, USAN, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



141 REFERENCES IN FILE CA (1967 TO DATE)
6 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
142 REFERENCES IN FILE CAPLUS (1967 TO DATE)

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=> fil medline caplus embase biosis uspatfull
=> s l1 or cetrorelix
L2          777 L1 OR CETRORELIX

=>

=>

=>

=> s endometri? and l2
L3           78 ENDOMETRI? AND L2

=> dup rem l3
PROCESSING COMPLETED FOR L3
L4            51 DUP REM L3 (27 DUPLICATES REMOVED)

=> s l4 range=,1999
',1999' IS NOT A VALID RANGE FOR FILE 'MEDLINE'
Valid RANGE values are file specific.  For more information, enter
HELP RANGE or HELP SET RANGE at an arrow prompt (=>) in the current
file.
ENTER RANGE FOR FILE 'MEDLINE' OR (ALL):end
SEARCH ENDED BY USER
L5           19 L4

=>
=> s l4 not py>1999
L6           21 L4 NOT PY>1999

=> d ibib abs kwic tot

L6   ANSWER 1 OF 21  MEDLINE
ACCESSION NUMBER:    2000149595      MEDLINE
DOCUMENT NUMBER:     20149595   PubMed ID: 10685334
TITLE:               LH-RH analogues: I. Their impact on reproductive medicine.
AUTHOR:              Schally A V
CORPORATE SOURCE:    Endocrine, Polypeptide and Cancer Institute, Veterans
                     Affairs Medical Center, New Orleans, Louisiana 70112-1262,
                     USA.
CONTRACT NUMBER:     AM-09094 (NIADDK)
                     CA-40003 (NCI)
                     DK-07467 (NIDDK)
                     +
SOURCE:              GYNECOLOGICAL ENDOCRINOLOGY, (1999 Dec) 13 (6) 401-9.  Ref:
                     81
                     Journal code: 125; 8807913. ISSN: 0951-3590.
PUB. COUNTRY:        ENGLAND: United Kingdom
                     Journal; Article; (JOURNAL ARTICLE)
                     General Review; (REVIEW)
                     (REVIEW, TUTORIAL)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         200003
ENTRY DATE:          Entered STN: 20000327
                     Last Updated on STN: 20000327
                     Entered Medline: 20000310
AB   In the 28 years that have passed since the elucidation of the structure of
     luteinizing hormone-releasing hormone (LH-RH), diverse clinical
     applications in the field of reproductive medicine and related fields have
     been established for agonists of LH-RH, based on inhibition of the
     pituitary-gonadal axis. Various clinical investigations with agonists of
     LH-RH in benign gynecologic disorders, polycystic ovary disease (PCOD), in
     vitro fertilization-embryo transfer (IVF-ET), benign prostatic hypertrophy
     (BPH), precocious puberty and contraception were reviewed. LH-RH
     antagonists inhibit LH, follicle-stimulating hormone (FSH), and sex
     steroid secretion immediately after their administration and thus achieve
     rapid therapeutic effects. LH-RH antagonists should find applications in
     the treatment of uterine leiomyomas, endometriosis, and in
     controlled ovarian stimulation-assisted reproductive techniques (COS-ART),
     which have been already established for the agonists. Modern LH-RH
     antagonists such as cetrorelix may prove superior to the
```

agonists in COS-ART and also in the treatment of BPH, but additional studies in these and other areas are needed.

CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
Contraception
Endometriosis: DT, drug therapy
*Gonadorelin: AA, analogs & derivatives
Polycystic Ovary Syndrome: DT, drug therapy
Prostatic Hyperplasia: DT, drug therapy

. . .

L6 ANSWER 2 OF 21 MEDLINE
ACCESSION NUMBER: 2000037969 MEDLINE
DOCUMENT NUMBER: 20037969 PubMed ID: 10573298
TITLE: Luteinizing hormone-releasing hormone analogs: their impact on the control of tumorigenesis.
AUTHOR: Schally A V
CORPORATE SOURCE: Endocrine, Polypeptide and Cancer Institute, Veterans Affairs Medical Center, and Department of Medicine, Tulane University School of Medicine, New Orleans, LA 70112, USA.
CONTRACT NUMBER: AM-09094 (NIADDK)
CA-40003 (NCI)
DK-07467 (NIDDK)
+
SOURCE: PEPTIDES, (1999) 20 (10) 1247-62. Ref: 185
Journal code: PA7; 8008690. ISSN: 0196-9781.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991223

AB The development of the luteinizing hormone-releasing hormone (LH-RH) agonists and antagonists and the principles of their clinical use were reviewed. In the 28 years that have elapsed since the elucidation of the structure of LH-RH, various applications in gynecology, reproductive medicine, and oncology have been established for LH-RH agonists and antagonists. These clinical applications are based on inhibition of the pituitary and the gonads. The advantage of the LH-RH antagonists is due to the fact that they inhibit the secretion of gonadotropins and sex steroids immediately after the first injection and thus achieve rapid therapeutic effects in contrast to the agonists, which require repeated administration. LH-RH antagonists should find applications in the treatment of benign gynecologic disorders and benign prostatic hypertrophy and in assisted reproduction programs. The primary treatment of advanced androgen-dependent prostate cancer is presently based on the use of depot preparations of LH-RH agonists, but antagonists like **Cetrorelix** already have been tried successfully. Antagonists of LH-RH might be more efficacious than agonists in treatment of patients with breast cancer as well as ovarian and **endometrial** cancer. Recently, practical cytotoxic analogs of LH-RH that can be targeted to LH-RH receptors on tumors have been synthesized and successfully tested in experimental cancer models. Targeted cytotoxic LH-RH analogs show a great promise for therapy of prostate, breast, and ovarian cancers.

L6 ANSWER 3 OF 21 MEDLINE
ACCESSION NUMBER: 96077434 MEDLINE
DOCUMENT NUMBER: 96077434 PubMed ID: 8567825
TITLE: Development and applications of luteinizing hormone-releasing hormone antagonists in the treatment of infertility: an overview.
AUTHOR: Reissmann T; Felberbaum R; Diedrich K; Engel J; Comaru-Schally A M; Schally A V
CORPORATE SOURCE: Clinic for Obstetrics and Gynaecology, University of Lubeck, Germany.
SOURCE: HUMAN REPRODUCTION, (1995 Aug) 10 (8) 1974-81. Ref: 62
Journal code: HRP; 8701199. ISSN: 0268-1161.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199603
ENTRY DATE: Entered STN: 19960315
Last Updated on STN: 19960315
Entered Medline: 19960307

AB Luteinizing hormone-releasing hormone (LHRH) plays a crucial role in controlling the ovarian cycle in women. By modification of the molecular structure of this decapeptide, analogues were synthesized with agonistic or antagonistic effects on the gonadotrophic cells of the anterior pituitary gland. The agonists, after an initial stimulatory effect ('flare up'), lead to desensitization of the gonadotrophic cells and a reduction in the number of LHRH receptors on the cell membrane ('down-regulation'), while the antagonists produce an immediate effect by competitive blockade of the LHRH receptors. After administration of LHRH antagonists, the serum levels of FSH and LH decrease within hours. Nevertheless, the adenohypophysis maintains its responsiveness to an LHRH stimulus ('pituitary response') after pretreatment with an antagonist. This different pharmacological mechanism of LHRH antagonists makes possible new approaches to ovarian stimulation and to the therapy of sex steroid dependent diseases. The premature LH surge, the main cause of cancellation during induction of superovulation in assisted reproduction technology (ART) programmes, can be abolished by short term application of an LHRH antagonist associated with a reduced human menopausal gonadotrophin (HMG) requirement for ovarian stimulation. A future approach to ART might be based on the combination of pretreatment with an LHRH antagonist and ovulation induction by native LHRH or an agonist. The severe side effects encountered with early LHRH antagonists, such as anaphylactoid reactions due to histamine release, are almost completely eliminated in modern antagonists, especially **Cetrorelix** which is presently used clinically in controlled phase II clinical studies.

CT Check Tags: Female; Human
Adult
Amino Acid Sequence
Endometriosis: DT, drug therapy
Gonadorelin: AG, agonists
*Gonadorelin: AI, antagonists & inhibitors
Gonadorelin: PH, physiology
Infertility, Female: PP, physiopathology
*Infertility,. . .

L6 ANSWER 4 OF 21 MEDLINE
ACCESSION NUMBER: 94127534 MEDLINE
DOCUMENT NUMBER: 94127534 PubMed ID: 8296852
TITLE: Direct growth inhibition of human **endometrial** cancer cells by the gonadotropin-releasing hormone antagonist SB-75: role of apoptosis.
AUTHOR: Kleinman D; Douvdevani A; Schally A V; Levy J; Sharoni Y
CORPORATE SOURCE: Department of Clinical Biochemistry, Faculty of Health Sciences, Ben-Gurion University of the Negev, Soroka Medical Center of Kupat Holim, Beer-Sheva, Israel.
SOURCE: AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, (1994 Jan) 170 (1 Pt 1) 96-102.
Journal code: 3NI; 0370476. ISSN: 0002-9378.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199403
ENTRY DATE: Entered STN: 19940314
Last Updated on STN: 19970203
Entered Medline: 19940301

AB OBJECTIVE: Our objective was to study the direct action of the gonadotropin-releasing hormone antagonist SB-75 and the agonist buserelin on the proliferation of **endometrial** cancer cells. STUDY DESIGN: Two human **endometrial** cell lines that differ in histologic subtype and estrogen receptor content were treated with gonadotropin-releasing hormone analog. We measured the number of viable cells, cell cycle parameters, and apoptotic processes. RESULTS: Growth of the Ishikawa cells was inhibited by SB-75 in a dose-dependent manner. 17 beta-Estradiol partially abolished the inhibitory effect of SB-75. The

growth of the HEC-1A cells was not affected by the antagonist. Neither **endometrial** cancer cell line showed significant sensitivity to the agonist buserelin. Tenfold concentration of the gonadotropin-releasing hormone agonist did not abolish the inhibitory effect of the antagonist on cell growth. The growth inhibition was not associated with any change in cell cycle parameters but was associated with an induction of apoptosis. CONCLUSION: The gonadotropin-releasing hormone antagonist SB-75 directly inhibits the growth of some human **endometrial** cancer cells and thus may be suitable for the treatment of **endometrial** tumors.

TI Direct growth inhibition of human **endometrial** cancer cells by the gonadotropin-releasing hormone antagonist SB-75: role of apoptosis.

suitable for the treatment of **endometrial** tumors.

CT . . .

Division: DE, drug effects
DNA, Neoplasm: AN, analysis
DNA, Neoplasm: IP, isolation & purification
Dose-Response Relationship, Drug
Electrophoresis, Agar Gel
Endometrial Neoplasms: CH, chemistry
***Endometrial Neoplasms: DT, drug therapy**
Endometrial Neoplasms: PA, pathology
Estradiol: PD, pharmacology
Flow Cytometry
*Gonadorelin: AA, analogs & derivatives
*Gonadorelin: AI, antagonists & inhibitors
Gonadorelin:. . .

RN **120287-85-6 (SB 75)**; 33515-09-2 (Gonadorelin); 50-28-2 (Estradiol); 57982-77-1 (Buserelin)

L6 ANSWER 5 OF 21 MEDLINE
ACCESSION NUMBER: 94089967 MEDLINE
DOCUMENT NUMBER: 94089967 PubMed ID: 8265821
TITLE: Regulation of **endometrial** cancer cell growth by insulin-like growth factors and the luteinizing hormone-releasing hormone antagonist SB-75.
AUTHOR: Kleinman D; Roberts C T Jr; LeRoith D; Schally A V; Levy J; Sharoni Y
CORPORATE SOURCE: Clinical Biochemistry Department, Faculty of Health Sciences, Ben-Gurion University of the Negev, Soroka Medical Center of Kupat Holim, Beer-Sheva, Israel.
SOURCE: REGULATORY PEPTIDES, (1993 Oct 20) 48 (1-2) 91-8. Journal code: RBB; 8100479. ISSN: 0167-0115.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199401
ENTRY DATE: Entered STN: 19940209
Last Updated on STN: 19970203
Entered Medline: 19940127

AB The involvement of IGFs in growth regulation of the Ishikawa **endometrial** tumor cell line and the possible interference of LH-RH analogues with a potential autocrine or paracrine loop involving IGFs was evaluated. The mitogenic effects of IGF-I, IGF-II, and insulin were compared. IGF-I was found to be 3-fold more potent than IGF-II and 30-fold more potent than insulin, suggesting that the effects of these growth factors are mediated by the IGF-I receptor. Ishikawa **endometrial** cancer cells secrete IGF-II, but not IGF-I, and insulin (1 microM) stimulates IGF-II release. The LH-RH antagonist [Ac-D-Nal(2)1, D-Phe(4Cl)2, D-Pal(3)3, D-Cit6, D-Ala10]-GnRH (SB-75, **CETRORELIX**) inhibited basal and IGF-induced growth. Moreover, this antagonist almost completely inhibited IGF-II release from Ishikawa cells, while having no significant effect on the number or affinity of IGF-I binding sites. Inhibition of IGF-II release occurred at a lower SB-75 concentration than that needed for a reduction in cell number. The ED50 of SB-75 for IGF-II release was 0.3 microM as compared to 1.5 microns concentration which is required for reduction in cell number, suggesting that inhibition of growth factor release precedes cell growth inhibition. We conclude that the LH-RH antagonist SB-75 can inhibit the growth of **endometrial** cancer cells by interfering with the autocrine action of IGF-II and also by directly inhibiting the growth-stimulatory effects of IGFs, probably through effects on a post-receptor mechanism.

TI Regulation of **endometrial** cancer cell growth by insulin-like

growth factors and the luteinizing hormone-releasing hormone antagonist SB-75.

CT Check Tags: Female; Human; Support, Non-U.S. Gov't
*Cell Division: DE, drug effects
Cell Line
Dose-Response Relationship, Drug
Drug Interactions
Endometrial Neoplasms
*Gonadorelin: AA, analogs & derivatives
*Gonadorelin: AI, antagonists & inhibitors
Gonadorelin: PD, pharmacology
*Insulin: PD, pharmacology
*Insulin-Like Growth. . .

RN 11061-68-0 (Insulin); **120287-85-6 (SB 75)**; 33515-09-2 (Gonadorelin); 67763-96-6 (Insulin-Like Growth Factor I); 67763-97-7 (Insulin-Like Growth Factor II)

L6 ANSWER 6 OF 21 MEDLINE
ACCESSION NUMBER: 94086728 MEDLINE
DOCUMENT NUMBER: 94086728 PubMed ID: 8263128
TITLE: High affinity binding and direct antiproliferative effects of luteinizing hormone-releasing hormone analogs in human **endometrial** cancer cell lines.
AUTHOR: Emons G; Schroder B; Ortmann O; Westphalen S; Schulz K D; Schally A V
CORPORATE SOURCE: Department of Obstetrics and Gynecology, Philipps University, Marburg, Germany.
SOURCE: JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, (1993 Dec) 77 (6) 1458-64.
Journal code: HRB; 0375362. ISSN: 0021-972X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199401
ENTRY DATE: Entered STN: 19940209
Last Updated on STN: 19970203
Entered Medline: 19940124

AB Although specific binding sites for LH-releasing hormone (LHRH) and its analogs have been demonstrated in biopsy samples of human **endometrial** cancer, their biological significance remains obscure. In this study we evaluated whether binding sites for LHRH are also present in the human **endometrial** cancer cell lines HEC-1A and Ishikawa and if such sites could mediate antiproliferative effects of LHRH analogs. Using [125I,D-Trp6]LHRH as a ligand, a high affinity/low capacity binding site was detected in both lines: HEC-1A line, dissociation constant (Kd)1 = 5.7 x 10(-9) mol/L, binding capacity (Bmax)1 = 78 fmol/10(6) cells; Ishikawa line, Kd1 = 4.2 x 10(-9) mol/L, Bmax1 = 29 fmol/10(6) cells. In addition, a second class of low affinity/high capacity binding sites for LHRH was demonstrated (HEC-1A line, Kd2 = 1.4 x 10(-6) mol/L, Bmax2 = 21 pmol/10(6) cells; Ishikawa, Kd2 = 4 x 10(-6) mol/L, Bmax2 = 32 pmol/10(6) cells). In the presence of 10(-5) mol/L agonist [D-Trp6]LHRH (triptorelin), the proliferation of HEC-1A and Ishikawa cell lines was significantly reduced to 76 +/- 2% and 88 +/- 4% of controls, respectively, after 24 h and to 64 +/- 2% and 62 +/- 2%, respectively, after 6 days. Dose-response experiments showed that lower concentrations (10(-9) mol/L) of the agonist decreased the proliferation to 80 +/- 1% for the HEC-1A line and 71 +/- 2% of controls for the Ishikawa line after 6 days. Antiproliferative effects are enhanced by increasing the doses of triptorelin and were maximal in this series of experiments at 10(-5) mol/L, the proliferation in the HEC-1A line being 62 +/- 1% and in the Ishikawa line 52 +/- 2% of controls, respectively. Similar time- and dose-dependent antiproliferative effects were obtained in both cell lines with the LHRH antagonist SB-75 (**cetrorelix**). These data suggest that LHRH analogs can directly inhibit the proliferation of human **endometrial** cancer cells in vitro. This direct action could be mediated through the high affinity LHRH binding sites.

TI High affinity binding and direct antiproliferative effects of luteinizing hormone-releasing hormone analogs in human **endometrial** cancer cell lines.

CT . . . Female; Human; Support, Non-U.S. Gov't
Amino Acid Sequence
Binding Sites

Cell Division: DE, drug effects
Dose-Response Relationship, Drug
Drug Stability
***Endometrial Neoplasms: DT, drug therapy**
Endometrial Neoplasms: ME, metabolism
Endometrial Neoplasms: PA, pathology
*Gonadorelin: AA, analogs & derivatives
*Gonadorelin: AI, antagonists & inhibitors
Gonadorelin: ME, metabolism
Gonadorelin: PD, pharmacology

RN **120287-85-6 (SB 75)**; 33515-09-2 (Gonadorelin); 57773-63-4 (Triptorelin)

L6 ANSWER 7 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:200802 CAPLUS
DOCUMENT NUMBER: 128:268963
TITLE: Presence and characteristics of receptors for [D-Trp6]luteinizing hormone releasing hormone and epidermal growth factor in human ovarian cancer
AUTHOR(S): Srkalovic, Gordan; Schally, Andrew V.; Wittliff, James L.; Day, Thomas G., Jr.; Jenison, Eric L.
CORPORATE SOURCE: Endocrine, Polypeptide and Cancer Institute, Veterans Affairs Medical Center and Department of Medicine, Tulane University Medical School, New Orleans, LA, USA
SOURCE: Int. J. Oncol. (1998), 12(3), 489-498
CODEN: IJONES; ISSN: 1019-6439
PUBLISHER: International Journal of Oncology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study was undertaken to establish the presence and characteristics of receptors for [D-Trp6]LH-RH on the membranes of human ovarian cancer. Specific binding of [125I, D-Trp6]LH-RH was found in 29 of 37 (78.4%) ovarian cancers and in 6 of 11 (54.5%) non-malignant human ovaries. Ligand binding was dependent on time and plasma membrane concn. in a fashion expected of a peptide hormone. Satn., kinetic and displacement data were consistent with the presence of a highly specific, single class of non-cooperative binding site. On the basis of receptors affinity, LH-RH-receptor-pos. ovarian cancers could be divided into two groups: high affinity group (Kd=2.71.+-.0.60 nM; Bmax=0.46.+-.0.07 pmol/mg membrane protein) comprising 55% of tumors, and low affinity group (Kd=78.0.+-.19.6 nM; Bmax=9.44.+-.2.68 pmol/mg membrane protein) which included 45% of tumors. LH-RH antagonist **Cetrorelix** showed an affinity to LH-RH receptors on ovarian cancers 14 times higher than the agonist [D-Trp6]LH-RH. Using 125I-epidermal growth factor, specific high affinity receptors were also detected in membranes from 13 of 24 (54%) ovarian cancers and 5 of 11 (45%) non-malignant ovaries. The demonstration of LH-RH receptors in human ovarian cancers provides a rationale for the use of therapeutic approaches based on LH-RH analogs in this malignancy. The probable involvement of growth factors in the development of ovarian cancers suggests the merit of trying a combined therapy based on analogs of LH-RH and somatostatin for this carcinoma.
IT Antitumor agents
Endometrial adenocarcinoma
Ovarian carcinoma
(LH-RH receptors and EGF receptors characterization in human ovarian cancer cells)
IT **120287-85-6, Cetrorelix**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(LH-RH receptors and EGF receptors characterization in human ovarian cancer cells)

L6 ANSWER 8 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:29519 CAPLUS
DOCUMENT NUMBER: 128:162903
TITLE: Antagonistic analogs of LHRH in oncology and gynecology
AUTHOR(S): Schally, A. V.; Comaru-Schally, A. M.; Gonzalez-Barcena, D.; Reissmann, T.; Engel, J.
CORPORATE SOURCE: UK
SOURCE: Int. Congr., Symp. Semin. Ser. (1997), 13(Endometriosis Today), 401-413

CODEN: ICGSEM; ISSN: 0969-2622
PUBLISHER: Parthenon Publishing Group Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 70 refs. LHRH antagonists, esp. **cetrorelix**, are reviewed along with their prospective clin. applicability to in vitro fertilization/embryo transfer, gynecol. oncol., fibroids, **endometriosis** and prostate disorders.

L6 ANSWER 9 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:707016 CAPLUS
DOCUMENT NUMBER: 128:18709
TITLE: Rational use of agonists and antagonists of luteinizing hormone-releasing hormone (LH-RH) in the treatment of hormone-sensitive neoplasms and gynecologic conditions
AUTHOR(S): Schally, Andrew V.; Maria Comaru-Schally, Ana
CORPORATE SOURCE: Endocrine, Polypeptide and Cancer Institute, VA Medical Centre and Section of Experimental Medicine, Department of Medicine, Tulane University School of Medicine, New Orleans, USA
SOURCE: Adv. Drug Delivery Rev. (1997), 28(1), 157-169
CODEN: ADDREP; ISSN: 0169-409X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 89 refs. Analogs of LH-releasing hormone (LH-RH) have made possible new approaches to the treatment of some hormone-dependent cancers and diseases and conditions which result from inappropriate sex hormone levels. In the fields of both gynecol. and oncol., the development of sustained delivery depot systems has played a key role in the clin. use of LH-RH agonists and will be also essential for the LH-RH antagonists. Clin. show that therapy with agonists of LH-RH is the preferred method of treatment for men with advanced prostate cancer. For prostate cancer and other indications, the new LH-RH antagonists such as **Cetrorelix** may offer an advantage based on the fact that they inhibit LH, FSH and sex-steroid secretion from the start of the administration and thus reduce the time of the onset of therapeutic effects. The use of antagonists would avoid the temporary clin. "flare-up" of the disease which can occur with the agonists in men with prostate cancer. The rapid shrinkage of the prostate and improvement in urinary symptoms obtained with **Cetrorelix** in men with benign prostatic hyperplasia (BHP) suggests that LH-RH antagonists offer a therapeutic alternative in patients who are considered poor surgical risks. Various exptl. and clin. studies suggest that analogs of LH-RH might be useful for treatment of premenopausal women with estrogen-dependent breast cancer. LH-RH antagonists such as **Cetrorelix** could be also considered for hormonal therapy of epithelial ovarian cancer which responds only marginally to the agonists, and for treatment of **endometrial** cancer. Many investigators have reported beneficial effects of LH-RH agonists in the treatment of patients with leiomyomas. LH-RH antagonists also appear to be promising for therapy of uterine leiomyomas, and in addn. might be useful for treatment of **endometriosis** and polycystic ovarian disease (PCOD). LH-RH agonists have been employed in in vitro fertilization and embryo transfer (IVF-ET) programs to prevent a premature rise in LH and various results suggest that the use of antagonist **Cetrorelix** in assisted reprodn. procedures, could be even more advantageous. For most of these indications, the use of sustained release depot prepns. will be required.

L6 ANSWER 10 OF 21 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998243707 EMBASE
TITLE: Effects of LHRH-analogues on mitogenic signal transduction in cancer cells.
AUTHOR: Emons G.; Muller V.; Ortmann O.; Schulz K.-D.
CORPORATE SOURCE: G. Emons, Dept. of Obstetrics and Gynecology, Philipps University, Pilgrimstein 3, D-35033 Marburg, Germany
SOURCE: Journal of Steroid Biochemistry and Molecular Biology, (1998) 65/1-6 (199-206).
Refs: 58
ISSN: 0960-0760 CODEN: JSBBEZ
PUBLISHER IDENT.: S 0960-0760(97)00189-1
COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The expression of luteinizing hormone-releasing hormone (LHRH) and its receptors has been demonstrated in a number of human malignant tumors, including cancers of the breast, ovary, **endometrium** and prostate. These findings suggest the presence of an autocrine regulatory system based on LHRH. Recent studies in our laboratory have demonstrated that the function of LHRH produced by ovarian cancer cells is the inhibition of their proliferation. Dose-dependent antiproliferative effects of LHRH-agonists have been observed by several laboratories in cell lines derived from the above cancers. Interestingly, also LHRH-antagonists have marked antiproliferative activity in most of the ovarian, breast and **endometrial** cancer cell lines tested so far, indicating that the dichotomy of LHRH-agonists/LHRH- antagonists is not valid for the LHRH-system in cancer cells. In addition, our data suggest that the classical LHRH receptor signal transduction mechanisms known from the pituitary (phospholipase-C, protein kinase C, adenylyl cyclase) are not involved in the mediation of LHRH effects in cancer cells. Data obtained by several groups, including ours, rather suggest that EaRn analogs interfere with the signal transduction of growth-factor receptors and related oncogene products associated with tyrosine-kinase activity. The mechanism of action is probably an LHRH-induced activation of a phosphotyrosine phosphatase, counteracting the effects of receptor associated tyrosine kinase. In our hands, LHRH analogs virtually blocked the EGF- induced MAP-kinase activity of ovarian and **endometrial** cancer cells. The pharmacological exploitation of this mechanism might provide promising new therapies for these cancers.

CT Medical Descriptors:
*hormonal regulation
*cancer cell: ET, etiology
cell proliferation
dose response
ovary cancer: ET, etiology
breast cancer: ET, etiology
endometrium cancer: ET, etiology
signal transduction
drug mechanism
human
human cell
conference paper
*gonadorelin derivative: PD, pharmacology
*gonadorelin agonist: PD, pharmacology
*protirelin: PD, pharmacology
*gonadorelin receptor: EC, endogenous compound
phospholipase c: EC, endogenous compound
protein kinase c: EC, endogenous compound
adenylate cyclase: EC, endogenous compound
protein tyrosine phosphatase: EC, endogenous compound
cetrorelix: PD, pharmacology

RN (protirelin) 24305-27-9; (phospholipase c) 9001-86-9; (protein kinase c) 141436-78-4; (adenylate cyclase) 9012-42-4; (protein tyrosine phosphatase) 79747-53-8, 97162-86-2; (**cetrorelix**) **120287-85-6**

L6 ANSWER 11 OF 21 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998054546 EMBASE
TITLE: Gonadotropin-releasing hormone and analogues in reproductive medicine.
AUTHOR: Cardamakis E.; Tzingounis V.; Keramida M.
CORPORATE SOURCE: Dr. V. Tzingounis, Department of Obstetrics/Gynecology, Medical School of Univ. of Patras, 265 10 Patra, Greece
SOURCE: Review of Clinical Pharmacology and Pharmacokinetics, International Edition, (1997) 11/2-3 (97-103).
Refs: 56
ISSN: 1011-6583 CODEN: EKIEE2
COUNTRY: Greece
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 010 Obstetrics and Gynecology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: English
CT Medical Descriptors:
***endometrium cancer: DT, drug therapy**
*breast fibroma: DT, drug therapy
*ovary hyperstimulation
***endometriosis: DT, drug therapy**
female infertility: DT, drug therapy
drug efficacy
hormonal therapy
osteoporosis: SI, side effect
drug indication
luteinizing hormone release
follitropin release
human
clinical trial
article
*gonadorelin: AE, adverse. . . PD, pharmacology
*gonadorelin derivative: AE, adverse drug reaction
*gonadorelin derivative: DT, drug therapy
*gonadorelin derivative: PD, pharmacology
luteinizing hormone: EC, endogenous compound
follitropin: EC, endogenous compound
cetrorelix: DT, drug therapy
danazol: DT, drug therapy
triptorelin: AE, adverse drug reaction
triptorelin: DT, drug therapy
leuprorelin: AE, adverse drug reaction
leuprorelin: DT, drug therapy
buserelin:. . .
RN (gonadorelin) 33515-09-2, 9034-40-6; (luteinizing hormone) 39341-83-8, 9002-67-9; (follitropin) 9002-68-0; (**cetrorelix**) **120287-85-6**; (danazol) 17230-88-5; (triptorelin) 57773-63-4; (leuprorelin) 53714-56-0, 74381-53-6; (buserelin) 57982-77-1; (nafarelin) 76932-56-4; (ethinylestradiol) 57-63-6; (cyproterone acetate) 427-51-0

L6 ANSWER 12 OF 21 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 96139165 EMBASE
DOCUMENT NUMBER: 1996139165
TITLE: [Development strategies for drugs in the therapy of hormone-dependent tumors].
ENTWICKLUNGSSTRATEGIEN FUR ARZNEISTOFFE ZUR THERAPIE HORMONABHANGIGER TUMOREN.
AUTHOR: Von Angerer E.
CORPORATE SOURCE: Institut fur Pharmazie, Universitat Regensburg, Universitatsstrasse 1,D-93040 Regensburg, Germany
SOURCE: Pharmazie in Unserer Zeit, (1996) 25/2 (74-84).
ISSN: 0048-3664 CODEN: PHUZBI
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
010 Obstetrics and Gynecology
016 Cancer
028 Urology and Nephrology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: German
CT Medical Descriptors:
*tumor: DT, drug therapy
breast carcinoma: DT, drug therapy
cancer chemotherapy
endometrium carcinoma: DT, drug therapy
female
human
male
prostate carcinoma: DT, drug therapy
review
*antiandrogen: DT, drug therapy
*antiestrogen: DT, drug therapy
*antigestagen: DT, drug therapy
*aromatase inhibitor: DT,. . . DT, drug therapy
buserelin: DT, drug therapy
bicalutamide: DT, drug therapy
droloxifene: DT, drug therapy

fadrozole: DT, drug therapy
finasteride: DT, drug therapy
flutamide: DT, drug therapy
cetrorelix: DT, drug therapy
goserelin: DT, drug therapy
idoxifene: DT, drug therapy
ketoconazole: DT, drug therapy
letrozole: DT, drug therapy
leuprorelin: DT, drug therapy
n butyl 11. . .

RN . . . diol) 129453-61-8; (aminoglutethimide) 125-84-8; (anastrozole) 120511-73-1; (atamestane) 96301-34-7; (buserelin) 57982-77-1; (bicalutamide) 90357-06-5; (droloxifene) 82413-20-5; (fadrozole) 102676-31-3; (finasteride) 98319-26-7; (flutamide) 13311-84-7; (**cetrorelix**) **120287-85-6**; (goserelin) 65807-02-5; (idoxifene) 116057-75-1; (ketoconazole) 65277-42-1; (letrozole) 112809-51-5; (leuprorelin) 53714-56-0, 74381-53-6; (n butyl 11 (3,17beta dihydroxyestra 1,3,5(10) trien 7alpha yl). . .

L6 ANSWER 13 OF 21 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95129571 EMBASE
DOCUMENT NUMBER: 1995129571
TITLE: **Cetrorelix**. D-20453 (as trifluoroacetate). D-20761 (as acetate). SB-75.
SOURCE: Drugs of the Future, (1995) 20/3 (299-300). ISSN: 0377-8282 CODEN: DRFUD4
COUNTRY: Spain
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 010 Obstetrics and Gynecology
016 Cancer
028 Urology and Nephrology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
TI **Cetrorelix**. D-20453 (as trifluoroacetate). D-20761 (as acetate). SB-75.
CT Medical Descriptors:
*antineoplastic activity
***endometrium cancer**
*fertilization in vitro
*hyperplasia: DT, drug therapy
*ovary cancer
*prostate cancer: DT, drug therapy
drug efficacy
drug safety
endometriosis
female
human
male
mouse
nonhuman
ovulation
short survey
subcutaneous drug administration
tumor cell
*gonadorelin antagonist: PD, pharmacology
*gonadorelin antagonist: DT, drug therapy
*gonadorelin antagonist: CM, drug comparison
cetrorelix: PD, pharmacology
cetrorelix: DT, drug therapy
cetrorelix: CM, drug comparison
lhrh [6 dextro tryptophan]: CM, drug comparison
unclassified drug
RN (**cetrorelix**) **120287-85-6**

L6 ANSWER 14 OF 21 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94237233 EMBASE
DOCUMENT NUMBER: 1994237233
TITLE: The use of luteinizing hormone releasing hormone agonists and antagonists in gynaecological cancers.
AUTHOR: Emons G.; Schally A.V.
CORPORATE SOURCE: Dept of Obstetrics and Gynecology, Philipps University,D-35037 Marburg, Germany

SOURCE: Human Reproduction, (1994) 9/7 (1364-1379).
ISSN: 0268-1161 CODEN: HUREEE
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 010 Obstetrics and Gynecology
016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The use of agonistic analogues of luteinizing hormone releasing hormone (LHRH) is an established therapy for hormone-dependent metastatic pre-menopausal breast cancer. Their mechanism of action in this disease is the suppression of ovarian oestrogen production (medical castration). In the treatment of post-menopausal metastatic breast cancer, LHRH agonists also have some effect, although minor, probably through a suppression of ovarian androgen production. Convincing evidence has been accumulated that LHRH analogues can directly inhibit the proliferation of breast cancer cells in vitro. The clinical impact of these findings, however, is still controversial. Experimental data and several pilot clinical trials suggest that in epithelial ovarian cancer and sex-cord-stromal tumours of the ovary, LHRH agonists might have antitumour activity through the suppression of gonadotrophin secretion (selective medical hypophysectomy). Phase m clinical trials, evaluating this hypothesis, are in progress. Direct antiproliferative effects of LHRH analogues on epithelial ovarian cancer cells have been demonstrated in vitro. In **endometrial** cancer, experimental and early clinical results support the concept of a direct antiproliferative activity of LHRH analogues. Recently, potent antagonistic analogues of LHRH, devoid of relevant side-effects have become available for clinical testing. These new antagonists might be superior to agonistic LHRH analogues with respect to the rapidity and efficacy of selective medical hypophysectomy and medical castration. Modern LHRH antagonists might also permit a better exploitation of direct antitumour effects. A further therapeutic improvement in gynaecological oncology might result from a combination of LHRH agonists or antagonists with other peptide hormone analogues such as agonists of somatostatin or antagonists of bombesin/gastrin releasing peptide which have antitumour activity. Since 50% of breast cancers and 80% of epithelial ovarian cancers and **endometrial** cancers have high affinity binding sites for LHRH, cytotoxic LHRH analogues might provide a targeted chemotherapy, which would be more efficacious and less toxic than conventional regimens.
CT Medical Descriptors:
*gynecologic . . . site
breast cancer: DT, drug therapy
breast metastasis: DT, drug therapy
cancer inhibition
cell proliferation
clinical trial
cytotoxicity
depression: SI, side effect
diabetes mellitus: SI, side effect
drug efficacy
drug mechanism
endometrium cancer: DT, drug therapy
endometrium cancer: RT, radiotherapy
endometrium cancer: SU, surgery
estrogen synthesis
female
gonadotropin release
hot flush: SI, side effect
human
hypertension: SI, side effect
leydig cell tumor: DT, drug therapy
male
nonhuman
obesity: SI, side effect
ovary. . .
releasing peptide: EC, endogenous compound
gestagen: DT, drug therapy
gestagen: CT, clinical trial
gestagen: AE, adverse drug reaction
gestagen: CB, drug combination

gonadorelin: EC, endogenous compound
cetrorelix: CT, clinical trial
cetrorelix: DT, drug therapy
cetrorelix: PD, pharmacology
goserelin: CT, clinical trial
goserelin: PD, pharmacology
goserelin: DT, drug therapy
goserelin: AE, adverse drug reaction
leuprorelin: DT, drug therapy
leuprorelin: CT, clinical trial
leuprorelin:. . .
RN. . . 566-48-3; (bombesin) 31362-50-2; (buserelin) 57982-77-1; (cisplatin) 15663-27-1, 26035-31-4, 96081-74-2; (doxorubicin) 23214-92-8, 25316-40-9; (gastrin releasing peptide) 74815-57-9, 80043-53-4; (gonadorelin) 33515-09-2, 9034-40-6; (**cetrorelix**) **120287-85-6**; (goserelin) 65807-02-5; (leuprorelin) 53714-56-0, 74381-53-6; (tamoxifen) 10540-29-1; (triptorelin) 57773-63-4; (vapreotide) 103222-11-3

L6 ANSWER 15 OF 21 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94179320 EMBASE
DOCUMENT NUMBER: 1994179320
TITLE: Introduction of LHRH-antagonists into the treatment of gynaecological disorders.
AUTHOR: Reissmann Th.; Diedrich K.; Comaru-Schally A.M.; Schally A.V.
CORPORATE SOURCE: Clinic Obstetrics and Gynaecology, University of Lubeck,Lubeck, Germany
SOURCE: Human Reproduction, (1994) 9/5 (767-769).
ISSN: 0268-1161 CODEN: HUREEE
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 010 Obstetrics and Gynecology
021 Developmental Biology and Teratology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
CT Medical Descriptors:
animal experiment
animal model
clinical trial
drug mechanism
drug receptor binding
endometriosis: DT, drug therapy
female
fertilization in vitro
follitropin release
gonadotropin release
gynecology
hormone release
human
human tissue
intramuscular drug administration
intranasal drug administration
leiomyoma: DT, drug therapy
luteinizing hormone release
male
nonhuman
ovary polycystic disease:. . .
therapy
clomifene: DT, drug therapy
clomifene: CM, drug comparison
gonadorelin: EC, endogenous compound
gonadorelin agonist: CM, drug comparison
gonadorelin agonist: DT, drug therapy
gonadorelin agonist: PD, pharmacology
cetrorelix: CT, clinical trial
cetrorelix: CM, drug comparison
cetrorelix: DT, drug therapy
cetrorelix: PD, pharmacology
cetrorelix: CB, drug combination
human menopausal gonadotropin: PD, pharmacology
human menopausal gonadotropin: CB, drug combination
RN (clomifene) 911-45-5; (gonadorelin) 33515-09-2, 9034-40-6; (

cetrorelix) **120287-85-6**; (human menopausal gonadotropin)
61489-71-2
CN Sb 75; **Cetrorelix**

L6 ANSWER 16 OF 21 USPATFULL
ACCESSION NUMBER: 1999:128511 USPATFULL
TITLE: Pharmaceutical formulations for sustained drug delivery
INVENTOR(S): Gefter, Malcolm L., Lincoln, MA, United States
Barker, Nicholas, Southborough, MA, United States
Musso, Gary, Hopkinton, MA, United States
Molineaux, Christopher J., Brookline, MA, United States
PATENT ASSIGNEE(S): Praecis Pharmaceuticals, Inc., Cambridge, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5968895		19991019
APPLICATION INFO.:	US 1996-762747		19961211 (8)

DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Richter, Johann
ASSISTANT EXAMINER: Delacroix-Muirheid, C.
LEGAL REPRESENTATIVE: Lahive & Cockfield, LLP, Mandragouras, Amy E., DeConti, Giulio A.
NUMBER OF CLAIMS: 32
EXEMPLARY CLAIM: 10
NUMBER OF DRAWINGS: 2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 775
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Sustained delivery formulations comprising a water-insoluble complex of a peptide and a carrier macromolecule are disclosed. The formulations of the invention allow for loading of high concentrations of peptide in a small volume and for delivery of a pharmaceutically active peptide for prolonged periods, e.g., one month, after administration of the complex. The complexes of the invention can be milled or crushed to a fine powder. In powdered form, the complexes form stable aqueous suspensions and dispersions, suitable for injection. In a preferred embodiment, the peptide of the complex is an LHRH analogue, preferably an LHRH antagonist, and the carrier macromolecule is an anionic polymer, preferably carboxymethylcellulose. Methods of making the complexes of the invention, and methods of using LHRH-analogue-containing complexes to treat conditions treatable with an LHRH analogue, are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . the luteinizing hormone releasing hormone receptor such that release of luteinizing hormone is inhibited. Examples of LHRH antagonists include Antide, **Cetrorelix**, compounds described in U.S. Pat. No. 5,470,947 to Folkers et al.; PCT Publication No. WO 89/01944 by Folkers et al.;. . .
DETD . . . include hormone-dependent cancers (including prostate cancer, breast cancer, ovarian cancer, uterine cancer and testicular cancer), benign prostatic hypertrophy, precocious puberty, **endometriosis**, uterine fibroids, infertility (through in vitro fertilization) and fertility (i.e., contraceptive uses).
DETD . . . hormone-dependent cancers, such as prostate cancer, breast cancer, ovarian cancer, uterine cancer and testicular cancer, benign prostatic hypertrophy, precocious puberty, **endometriosis** and uterine fibroids. Accordingly, the invention provides methods of treating these diseases and disorders by administering a pharmaceutical formulation of. . .
IT 9000-07-1D, Carrageenan, anionic derivs. 9004-32-4 9005-32-7, Alginic acid 9005-38-3, Algin 9034-40-6D, LHRH, analogs 9046-38-2, Polygalacturonic acid 9063-38-1, Sodium starch glycolate 11138-66-2, Xanthan gum **120287-85-6**, Cetrorelix 183552-38-7, PPI 149 209122-72-5 209122-73-6
(pharmaceutical formulations for sustained drug delivery of peptides)

L6 ANSWER 17 OF 21 USPATFULL
ACCESSION NUMBER: 1999:81921 USPATFULL
TITLE: GnRH antagonists
INVENTOR(S): Semple, Graeme, Hampshire, United Kingdom
Jiang, Guangcheng, San Diego, CA, United States
PATENT ASSIGNEE(S): Ferring BV, Hoofddorp, Netherlands (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5925730		19990720	
APPLICATION INFO.:	US 1997-837042		19970411	(8)

DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Hill, Jr., Robert J.
ASSISTANT EXAMINER: Delacroix-Muirheid, C.
LEGAL REPRESENTATIVE: Fitch, Even, Tabin & Flannery
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1
LINE COUNT: 1458
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Peptides are provided which have improved duration of GnRH antagonistic properties. These antagonists may be used to regulate fertility and to treat steroid-dependent tumors and for other short-term and long-term treatment indications. These antagonists have a derivative of aminoPhe or its equivalent in the 5- and/or 6-positions. This derivative contains a carbamoyl group or a heterocycle including a urea in its side chain. Particularly effective decapeptides, which continue to exhibit very substantial suppression of LH secretion at 96 hours following injection, have the formulae: Ac-D-2Nal-D-4Cpa-D-3Pal-Ser-4Aph(hydroorotyl)-D-4Aph(acetyl)-Leu-Lys(isopropyl)-Pro-D-Ala-NH.sub.2, and Ac-D-2Nal-D-4Cpa-D-3Pal-Ser-4Aph(hydroorotyl)-D-4Amf(Q.sub.2)-Leu-Lys(isopropyl)-Pro-D-Ala-NH.sub.2, wherein Q.sub.2 is Cbm or MeCbm.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . of ovulation for in vitro fertilization. For example, GnRH antagonists may be used for the treatment of precocious puberty and **endometriosis** and other such conditions which result from hypersecretion of gonadotropins, and they are also useful for regulating the secretion of. . .

SUMM (10) interval treatment of **endometrial** cancer between diagnosis and surgery.

SUMM (3) **endometrial** cancer;

SUMM (7) **endometriosis**;

SUMM . . . improved GnRH antagonists has resulted in the making of Antide, i.e. [Ac-D-2Nal.sup.1, D-4ClPhe.sup.2, D-3Pal.sup.3, Lys(Nic).sup.5, D-Lys(Nic).sup.6, ILys.sup.8, D-Ala.sup.10]-GnRH; and **Cetrorelix**, i.e. [Ac-D-2Nal.sup.1, D-4ClPhe.sup.2, D-3Pal.sup.3, D-Cit.sup.6, D-Ala.sup.10]-GnRH. U.S. Pat. No. 5,516,887 describes GnRH antagonists which are said to be more. . .

SUMM . . . other modifications to the 5-position residue, or the 5- and 6-position residues, in this subclass of GnRH antagonists, which includes **Cetrorelix**, Antarelix, Acyline, Antide and others, unexpectedly result in compounds which when administered sc exhibit the particularly advantageous property of long. . .

SUMM . . . mammals, especially humans, as fertility regulators and for the treatment of pathological conditions such as precocious puberty, hormone-dependent neoplasia, dysmenorrhea, **endometriosis**, steroid-dependent tumors, and the other short-term and long-term indications mentioned hereinbefore. They are also useful diagnostically.

DETD The peptide [4Aph(Hor).sup.5, D-Cit.sup.6]-Antide, an analog of the peptide **Cetrorelix** having the formula Ac-D-2Nal-D-4Cpa-D-3Pal-Ser-4Aph(hydroorotyl)-D-Cit-Leu-ILys-Pro-D-Ala-NH.sub.2 is synthesized using the synthesis as generally set forth in Example 1. Instead of coupling N.sup..alpha.. . .

DETD The peptide is more hydrophilic than **Cetrorelix** and exhibits as long duration of bioactivity as **Cetrorelix** when tested in vivo for suppression of LH secretion as in Example 1. It has marginally better suppression at 3. . .

DETD . . . in Example 1. The peptide Ac-D-2Nal-D-4Cpa-D-3Pal-Ser-4Aph(hydroorotyl)-D-Lys(Nic)-Leu-ILys-Pro-D-Ala-NH.sub.2 is obtained in the RP-HPLC purification. It is considered to be more hydrophilic than **Cetrorelix** and to exhibit as long duration of bioactivity as **Cetrorelix** for suppression of LH secretion.

L6 ANSWER 18 OF 21 USPATFULL
ACCESSION NUMBER: 1998:124554 USPATFULL
TITLE: GnRH antagonist decapeptides
INVENTOR(S): Jiang, Guangcheng, San Diego, CA, United States
Semple, Graeme, Hamphire, United Kingdom
PATENT ASSIGNEE(S): Ferring BV, Hoofddorp, Netherlands (non-U.S.

corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5821230		19981013	
APPLICATION INFO.:	US 1997-837041		19970411	(8)

DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Tsang, Cecilia J.
ASSISTANT EXAMINER: Wang, Cecilia F.
LEGAL REPRESENTATIVE: Fitch, Even, Tabin & Flannery
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
LINE COUNT: 1630
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Peptides are provided which have improved duration of GnRH antagonistic properties and/or which can be synthesized more economically. These antagonists may be used in the same manner as the compounds of which they are analogs to regulate fertility and to treat steroid-dependent tumors and for other short-term and long-term treatment indications. One particularly effective peptide, a decapeptide analog of the GnRH antagonist Acyline, has the formula: Ac-D-2Nal-D-4Cpa-D-Dpr(methylcarbamoyl)-Ser-4Aph(acetyl)-D-4Aph(acetyl)-Leu-Lys(isopropyl)-Pro-D-Ala-NH.sub.2. It continues to exhibit very substantial suppression of LH secretion at 96 hours following injection. Other economically attractive and pharmacologically effective analogs have the formulas: Ac-D-2Nal-D-4Cpa-Xaa.sub.3 -Ser-4Aph(acetyl)-D-4Aph(acetyl)-Leu-Lys(isopropyl)-Pro-D-Ala-NH.sub.2 ; and Ac-D-2Nal-D-4Cpa-Xaa.sub.3 -Ser-4Aph(hydroorotyl)-D-4Aph(acetyl)-Leu-Lys(isopropyl)-Pro-D-Ala-NH.sub.2, wherein Xaa.sub.3 is D-Gln or Gln.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . of ovulation for in vitro fertilization. For example, GnRH antagonists may be used for the treatment of precocious puberty and **endometriosis** and other such conditions which result from hypersecretion of gonadotropins, and they are also useful for regulating the secretion of. . .

SUMM (10) interval treatment of **endometrial** cancer between diagnosis and surgery.

SUMM (3) **endometrial** cancer;

SUMM (7) **endometriosis**;

SUMM . . . improved GnRH antagonists has resulted in the making of Antide, i.e. [Ac-D-2Nal.sup.1, D-4ClPhe.sup.2, D-3Pal.sup.3, Lys(Nic).sup.5, D-Lys(Nic).sup.6, ILys.sup.8, D-Ala.sup.10]-GnRH; and **Cetrorelix**, i.e. [Ac-D-2Nal.sup.1, D-4ClPhe.sup.2, D-3Pal.sup.3, D-Cit.sup.6, D-Ala.sup.10]-GnRH. U.S. Pat. No. 5,516,887 describes GnRH antagonists which are said to be more. . .

SUMM . . . of less expensive residues, the cost can be reduced without reducing biopotency or this subclass of GnRH antagonists which includes **Cetrorelix**, Antarelix, Acyline, Azaline B, Antide and others. Not only are these analogs less expensive to synthesize than peptides containing the. . .

SUMM . . . mammals, especially humans, as fertility regulators and for the treatment of pathological conditions such as precocious puberty, hormone-dependent neoplasia, dysmenorrhea, **endometriosis**, steroid-dependent tumors, and the other short-term and long-term indications mentioned hereinbefore. They are also useful diagnostically.

DETD An analog of the peptide **Cetrorelix** having the formula Ac-D-2Nal-D-4Cpa-D-Dpr(methylcarbamoyl)-Ser-Tyr-D-Cit-Leu-Arg-Pro-D-Ala-NH.sub.2 is synthesized using the synthesis as generally set forth in Example 1. Instead of coupling N.sup..alpha.. . .

DETD . . . is considered to be more hydrophilic than Acyline and to have longer duration of in vivo suppression of LH than **Cetrorelix**.

L6 ANSWER 19 OF 21 USPATFULL
ACCESSION NUMBER: 1998:98932 USPATFULL
TITLE: DHA-pharmaceutical agent conjugates of taxanes
INVENTOR(S): Shashoua, Victor E., Brookline, MA, United States
Swindell, Charles S., Merion, PA, United States
Webb, Nigel L., Bryn Mawr, PA, United States
Bradley, Matthews O., Laytonsville, MD, United States
PATENT ASSIGNEE(S): Neuromedica, Inc., Conshohocken, PA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5795909		19980818	
APPLICATION INFO.:	US 1996-651312		19960522	(8)

DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Jarvis, William R. A.
LEGAL REPRESENTATIVE: Wolf, Greenfield & Sacks, P.C.
NUMBER OF CLAIMS: 12
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 27 Drawing Figure(s); 14 Drawing Page(s)
LINE COUNT: 2451
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides conjugates of cis-docosahexaenoic acid and taxanes useful in treating cell proliferative disorders. Conjugates of paclitaxel and docetaxel are preferred.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . treating diabetes and its complications, excess acid secretion, cardiovascular conditions involving cholesterol (e.g., hyperlipidemia and hypercholesterolemia), diarrhea, ovarian diseases (e.g. **endometriosis**, ovarian cysts, etc.) and as contraceptive agents. Other conditions treatable according to the invention will be apparent to those skilled. . .

DETD . . . canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; **cetrorelix**; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816;. . .

DETD . . . treating diabetes and its complications, excess acid secretion, cardiovascular conditions involving cholesterol (e.g., hyperlipidemia and hypercholesterolemia), diarrhea, ovarian diseases (e.g. **endometriosis**, ovarian cysts, etc.) and as contraceptive agents.

L6 ANSWER 20 OF 21 USPATFULL
ACCESSION NUMBER: 1998:75185 USPATFULL
TITLE: Long-acting injection suspensions and a process for their preparation
INVENTOR(S): Engel, Jurgen, Alzenau, Germany, Federal Republic of
Klokkers-Bethke, Karin, Lenggries, Germany, Federal Republic of
Reissman, Thomas, Frankfurt, Germany, Federal Republic of
Hilgard, Peter, Frankfurt, Germany, Federal Republic of
PATENT ASSIGNEE(S): Asta Medica Aktiengellschaft, Dresden, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5773032		19980630	
APPLICATION INFO.:	US 1996-661017		19960610	(8)

DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Azpuru, Carlos A.
LEGAL REPRESENTATIVE: Cushman Darby & Cushman IP Group of Pillsbury Madison & Sutro LLP
NUMBER OF CLAIMS: 8
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Figure(s); 4 Drawing Page(s)
LINE COUNT: 373
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Poorly soluble salts of LHRH analogues, for example **cetrorelix** embonate, display an intrinsic sustained release effect in the grain size 5 .mu.m to 200 .mu.m.

SUMM . . . analogs are understood to be both superagonists such as goserelin (INN) or triptorelin (INN), as well as antagonists such as **cetrorelix** (INN), antide (INN) or ganirelix (INN). Goserelin, and the synthesis of goserelin, is described in Drugs of the Future, 5. . .

SUMM . . . flare up, which has to be counteracted with additional medication. In contrast, in the case of the antagonists of which **cetrorelix** (INN) is one, the pharmacological effect occurs

immediately and there is no flare up. Lasting reduction in the sex hormone. . . . of prostate carcinoma and mamma carcinoma to reduce tumour growth in sex hormone-dependent tumours and also a curative treatment in **endometriosis**. Chemically speaking, the LHRH-superagonists and the antagonists are nona-or decapeptides.

SUMM An LHRH antagonist that is effective in the above indication is **cetrorelix**, a decapeptide of the amino acid sequence Ac-DNal-DpCl-Phe-DPal-Ser-Tyr-DCit-Leu-Arg-Pro-D-Ala-NH.sub.2. Its synthesis and pharmacological properties are described in EP 299 402. **Cetrorelix** acetate has been identified as the physiologically acceptable salt. It was found in preclinical and clinical studies that the aqueous solution of **cetrorelix** acetate had to be applied daily in order to lower the hormone level of testosterone or oestradiol to the appropriate. . .

SUMM DE-OS 42 23 282.1 describes the preparation of a sustained release formulation of **cetrorelix** embonate by microencapsulation. Implants are medicinal forms permitting longer intervals of use. For example, when implanted under the skin, a. . .

DRWD FIG. 2 Effect of administration of **Cetrorelix**, 0.5 mg/kg s.c. on testosterone levels in male rats. D20762 (in situ) precipitate without viscous additives.

DRWD FIG. 3 Effect of administration of **Cetrorelix**, 0.5 mg/kg s.c. on testosterone levels in male rats. D-20762 Microparticles RCSES 91-08.

DETD . . . the tumour weight for the untreated control animals shows uninhibited increase. Curves 1 (*) and 2 (0) show treatment with **cetrorelix** acetate in two different carriers. The extended curve 3 shows the drastic reduction in tumour weight after embonate treatment.

DETD The formulation of the invention is an X-ray amorphous precipitate of the decapeptide **cetrorelix** as an embonic acid salt. The aqueous suspension of this precipitate, which may optionally contain isotonifying additives, showed a marked. . .

DETD . . . to be amorphous. The particle size of the formulation of the invention lies between 5 um and 200 um. A **cetrorelix** embonate with a particle size under 5 um showed a sustained release effect inferior to that of the formulation of the invention. Similarly, a **cetrorelix** embonate with a particle size of more than 200 um showed a poorer sustained release effect than the formulation of. . .

DETD . . . free base) to embonic acid, an aqueous solution of embonic acid containing alkali in excess is combined with the acetate **cetrorelix** acetate solution, embonic acid precipitating as yellow crystals. On addition of dilute sodium hydroxide solution up to pH 7-7.5, the embonic acid dissolves and precipitates with the decapeptide as aqueous **cetrorelix** embonate salt of the molar composition peptide: embonic acid 2:1 (Mol/Mol). The precipitate is filtered off, washed with H.sub.2 O. . .

DETD **Cetrorelix** acetate and embonic acid are dissolved in equimolar proportions in dimethylacetamide and the solution is dropped into water. The white precipitate of the **cetrorelix** embonate peptide: embonic acid 2:1 (Mol/Mol) is filtered off and dried.

DETD **Cetrorelix** and embonic acid are dissolved in a molar ratio of 1:1.6 in a mixture of dimethyl acetamide and optionally water. . .

DETD Suspensions of the precipitates were applied subcutaneously to male rats in the dose 0.5 mg **cetrorelix**/kg body weight and determined after application as a measure of the effect of the peptide on testosterone plasma levels. The effect of the **cetrorelix** consists in reduction of the testosterone level. As a reference an injection suspension was tested as well, that prepared according. . . the peptide embonate in poly(lactic acid, glycolic acid) copolymers. The duration of action of a non-sustained release dosage form of **cetrorelix** was determined via examination of the aqueous solution of **cetrorelix** acetate.

DETD . . . the course of the testosterone level over 300 h determined in male rats after application of the aqueous solution of **cetrorelix** acetate (D-20761). The effect of testosterone suppression is achieved 6 h after the application. Suppression under 1 ng/ml could still. . .

DETD FIG. 2 shows the testosterone level over 300 h in four animals (No. 11-14) after applying the same dose of **cetrorelix** as a suspension of **cetrorelix** embonate (D-20762) without viscous additives prepared according to Example 1 (D-20762). The testosterone suppression is also achieved 6 h after. . .

CLM What is claimed is:

. . . particles lies between 5 and 200 .mu.m, characterized in that the

LHRH analogue is selected from the group consisting of **cetrorelix**, antarelix, ganirelix, antide and A-75998 which is not in the form of particles or microcapsules of a homopolymer or copolymer. . .

L6 ANSWER 21 OF 21 USPATFULL

ACCESSION NUMBER:	97:78416 USPATFULL
TITLE:	Products for administering an initial high dose of **Cetrorelix** and producing a combination package for use when treating diseases
INVENTOR(S):	Engel, Jurgen, Alzenau, Germany, Federal Republic of Hilgard, Peter, Frankfurt, Germany, Federal Republic of Reissmann, Thomas, Frankfurt, Germany, Federal Republic of
PATENT ASSIGNEE(S):	ASTA Medica Aktiengesellschaft, Dresden, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5663145		19970902
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PRIMARY EXAMINER:	Russel, Jeffrey E.
LEGAL REPRESENTATIVE:	Cushman Darby & Cushman IP Group of Pillsbury Madison & Sutro LLP
NUMBER OF CLAIMS:	25
EXEMPLARY CLAIM:	7
LINE COUNT:	227

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB For application during the treatment of benign and malign tumour diseases, the product according to the invention containing the initial dose of **Cetrorelix** acetate and one or more maintenance doses of **Cetrorelix** acetate, **Cetrorelix** embonate or a slow-release form of **Cetrorelix**, is used as a combination preparation for treatment to be administered at specific time intervals.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Products for administering an initial high dose of **Cetrorelix** and producing a combination package for use when treating diseases

DETD **Cetrorelix** (INN) is an antagonist for LHRH. The mode of action is completely different from that of the known superagonists. Synthesis. . . few important pharmacological effects are described in EP 299 402. This indicates that different doses are required for treatment with **Cetrorelix**.

DETD . . . purposes are initially placed in another glass vessel and 91.17 g of acetic acid are added. The calculated amount of **Cetrorelix** acetate (1.62-1.695 g. depending on the concentration of the feedstock used) is dissolved with stirring in the prepared 30% strength. . .

DETD . . . size 0.2 .mu.m, under aseptic conditions). The first 100 ml are discarded. The filters are sterilised with steam under pressure. **Cetrorelix** solution for freeze-drying is stored under protection against recontamination. The solution is immediately metered into DIN 2R injection vials which. . .

DETD **Cetrorelix** lyophilisate 1 mg is a white, solid freeze-dried cake in a colourless 2 ml injection phial which is sealed with. . .

DETD An aqueous solution of embonic acid containing excess alkali is combined with the acetic acid **Cetrorelix** acetate solution at an equimolar ratio of peptide (calculated as free base) to embonic acid, wherein the embonic acid precipitates. . . caustic soda solution until the pH is 7-7.5, the embonic acid dissolves and precipitates with the decapaptide as a white **Cetrorelix** embonate salt with the molar composition peptide:embonic acid of e.g. 2:1 (mol/mol). The precipitate is filtered off, washed with H.sub.2. . .

DETD A container or several containers are filled with the initial dose of **Cetrorelix** acetate lyophilisate. The amount used is between 1 mg and 60 mg of lyophilisate per container.

DETD Up to 30 further containers are filled with the maintenance dose of **Cetrorelix** acetate lyophilisate. The amount used is between 0.1 and 30 mg per container.

CLM What is claimed is:

3. The kit of claim 1, wherein the LHRH antagonist is **Cetrorelix**.

4. The kit of claim 3, wherein the initial dose of **Cetrorelix** is between about 1 and about 60 mg.

5. The kit of claim 3, wherein the maintenance dose of **Cetrorelix** is between about 0.1 and about 60 mg.

6. The kit of claim 3, wherein the maintenance dose of **Cetrorelix** consists of a slow-releasing formulation.

9. The method of claim 7, wherein the LHRH antagonist is **Cetrorelix**.

10. The method of claim 7, wherein **Cetrorelix** of the maintenance dose consists of a slow-releasing formulation.

11. The method of claim 9, wherein the initial dose of **Cetrorelix** is between about 1 and about 60 mg, and the maintenance dose of **Cetrorelix** is between about 0.1 and about 30 mg.

12. The method of claim 11, wherein the **Cetrorelix** of the maintenance dose consists of a slow-releasing formulation.

14. The method of claim 7, wherein the hormone-dependent condition is **endometrial** hyperplasia.

22. The method of claim 21, wherein the LHRH antagonist is **Cetrorelix**.

23. The method of claim 21, wherein the **Cetrorelix** of the maintenance dose consists of a slow-releasing formulation.

24. The method of claim 22, wherein the initial dose of **Cetrorelix** is between about 1 and 60 mg, and the maintenance dose of **Cetrorelix** is between about 0.1 and 30 mg.

25. The method of claim 24, wherein the **Cetrorelix** of the maintenance dose comprises **Cetrorelix** pamoate or **Cetrorelix** acetate in a slow-releasing form.

IT **120287-85-6**, Cetrorelix 145672-81-7 145672-82-8
(combined package for application of high initial doses of cetrorelix and lower maintenance doses)